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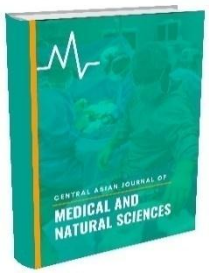

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Assessment of Biological and Anti-Cancer Activity, Design of Some Novel Heterocyclic Compounds, And Synthesis Based on Indole-Dione

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Abstract: This search included synthesized new hertocyclic derivatives from Isatin (T) via reaction with 4-aminobenzoic acid to give (T2), and with SOCl2 to give compound (T1), esterfication to give (T3), reacted with hydrazine to give (T4) compound, and with anhydrides to give (T5,T6). The schiff base (T10) prepared from benzylaldehyde and (T9) perpared fram (T2) and thiocarbohydrazide. (T8) compound synthesized fram (T2) and semicarbzide by aring closer reaction in NaOH. This (T1-T10) compounds were measured biological and anticancer activity and give high good activity with (IC50=42.18,45.02 for compounds 12 and 3).

Key words: Isatin, Hydrazin, Thiocarbohydrazide, Anticancer activity, Semicarbzide.

1. Introduction

Indoles are heterocyclic compounds that have a large number of pathological applications, such as cancer, microbial and viral infections, depression, vomiting, and high blood pressure. They are also used in perfumes (1). One of its derivatives is indole-2,3-dione (Isatin). It contains tuberculosis-fighting qualities (2).

Isatin are important compounds in medicinal chemistry and possess a wide range of biological activities and chemical synthesis. For example, anti-cancer (3). Also, its derivatives, such as thiazolidinedione, are an important part of medicinal chemistry for developing anti-cancer treatments (4,5).

Heterocyclic Schiff bases are among the preferred compounds in the medical field and medicine. It is used in organic synthesis (6,7).Medical uses for Schiff's isatin bases include antioxidants (8), anti-coagulation (9), plasmodia (10), diabetes (11), HIV, anti-inflammatory and anti-cancer(12-15).

1,2,4-Triazoles compounds are widely involved with pharmacological activities such as antibacterial,Antifungal, anticarcinogenic and anticonvulsant properties(13-19).

In the study, acetin was reacted with triazole , Schiff's rules are for the purpose of giving results best as antimicrobials in low concentration

2. Materials and Method

2.1. General

A new compounds (T1-T10) were prepared via Isatin with (4-aminobenzoic acid in ethanol ,then with different anhydride to form imides compounds (Scheme 1).

Isatin and other chemicals were obtained from Fluka,CDH and BDH . Identified compounds by FTIR, 1H and 13C NMR, "Testseon Shimadzu (FT- IR 8400Series Japan)". 1H NMR and 13C NMR((Bruker,UltraShield 500 MHZ and 100 MHz).

2.2.1. Synthesis of compound (T1)

- Isatin (0.02g, 0.065mol) was added to 4-aminobenzoic acid (0.0087 g, 0.065mol)

in 50 ml absolute ethanol, refluxed (10 hours), T.L.C (ethyl acetate :hexane 1:3) to reaction completed, then filtered , washed with water, recrystallized from ethanol (20) . The physical data in (Table 1).

The FT-IR spectrum(cm-1,vmax): compound [T1] Fig (1) and Table (1):

(3251-2999) OH acid , (3191) NH, (1616) C=N ,(1739) C=Oisatin. , (1688) C=O of carboxylic group. (1598) C=C ar. .

1HNMR (500MHz,DMSO-d6, ppm) :12.9 (s,1H,OH), 10.9(s,1H,NH), 7.8-6.3) (m,8H,Ar-H).

13C NMR(DMSO-d6, ppm): 112.12-155.01 (Ar-C), 155.55(C=N),163.69(C=O), 167.43(COOH).

2.2.2. Synthesis of compound (T2)

Compound (T1) (0.029.gm, 0.01.mol) in $SOCl_2$(30.mL), refluxed (80°C for 2 hrs. , recrystallized from DCM (21). The physical data in (Table 1).

FT-IR(compound T2): 3212(NH),3070(CH ar.) ,1756(COCl),1577(C=N), 1421 (C=C), (1196) C-O, 1349(C-N),(646)C-Cl.

2.2.3. Synthesis of Ester (T3)

Compound T2 (2.9 g, 0.01 mol), ethanol (15ml) ,H_2SO_4 (5 drop), ref. (2-5)h. the yield extracted with chloroform after the solvent removed, dried anhydrous Na2SO4 to give ester (1.90g) (22). (Table 1).

FTIR: 3015(CH ar.) ,2998(CH al.),1683(C=O),1132-1257) C-O, 1387(C-N).

1HNMR : 3.9(t,2H,CH2),1.9(d,3H,CH3),10.2 (s,1H-NH),6.5-7.9(m,8H,Ar-H.).

2.2.4. Synthesis of Isatin Hydrazide (T4)

Ester (T3) (2.94 g, 0.01 mol) in THF (10 mL), hydrazine (1 mL, 0.12 mol) was added , 3-4h.ref. , (50 mL) water add to reaction , filtered, washed and recrys-tallized in ethanol. (23)(Table 1).

FTIR : 3053 (C-H ar.), 1736 (C=O), 3107 (NH), 3385 (NH2), 1619 (C=N) ,1536(C=C),1142-1286)C-O , 1331(C-N).

1HNMR : 2.4(d,2H,NH2),10.6,8.4(s,1H-NH),6.5-7.9(m,8H,Ar-H.).

2.2.5. Synthesis of compound (T5,T6)

(0.01mol,0.89g) of compound (T4) mixed with different anhydride , heated in oil bath at (180-185)^{0}C for 30 minutes. The solid was cooled and recrystallzed with ethanol (24) .(Table 1).

FTIR (compound T5): 3257 (NH), 3082(CH ar.), 1704 (C=O), 1623 (C=N), 1172-1200 (C-O), 1503 (C=C), 1342(C-N).

1H NMR: δ 11.0 ,9.4 (s,2H,NH), 6.9-7.6 (m,12H, Ar).

FTIR (compound T6): 3253 (NH),3052 (CH ar.), 1736 (C=O), 1649 (C=N), 1175-1253 (C-O-C), 1618, 1459 (C=C) ,1331 C-N).

2.2.6. Synthesis of compound (T7)

Compound (T2) (0.01 mol) was added (1.82 g) of semicarbazide with 50 ml of sodium hydroxide solution (10%) mixed withstirring for 20 minutes , ice water added , (25) (Table 1).

FTIR: (3424,3251)(NH2) ,3191(NH) , (1700) (C=O) ,(3071) (CHar.) ,1622 (C=N),(1598-1505)(C=C), (1334)(C-N), (1163-1283)(C-O).

1HNMR: (6.3-7.8) $(CH)_{ar.}$, (10.9, 9.9) (NH), (5.89) (NH_2).

2.2.7.Synthesis of compound (T8)

A mixture of compound (T7), (0.01 mole, 0.473gm) dissolved in (50 ml dioxane) and added sodium hydroxide 4% (0.01 mole,) was stirred (4h.).,then added conc.HCl to acidified, the sloid was recrystallized from absolute ethyl alcohol.(26)

FTIR of (T8): 3224 (OH), 1700 (C=O), 3070(CHar),1621 (C=N) , 1602,1582 (C=C), 1342 (C-N) , (1125-1263) C-O,

1HNMR : 6.8-8.4 (CHar.) , 10.1(OH),10.78 (NH) .

13CNMR : (122.6-125.8)(CHar.) ,153.3 (C-OH) , 166.8(C=O),138.8(C=N).

2.2.8. Synthesis of compound (T9)

Compound (T2) (0.28g,0.01mol.) and thiocarbohydrazide (1.06g, 0.015mol.) , heat the mixture until it melts. Refrigerated product adding a solution of sodium bicarbonate to the equation Wash with water and filter. T.L.C to complete the reaction (hexane: ethyl acetate 1:2). Recrystallization of(ethanol)(27).

FTIR (compound T): 3448 (NH_2), 3395(NH),1568(C=N),1655(C=O), 1415 (C=Car.).

1HNMR: δ 13.01 (s,1H,SH), 11.33 (s,1H,NH), 7.62-6.54 (m,8H,Ar-H) , 5.87 (s,2H,NH2) .

2.2.9. Synthesis of compounds (T10)

Compound (T9) (0.33 gm, 0.01 mol) , (benzylldehyde (0.35 mol), conc. H2SO4 (2-3 drops) and ethanol (15 mL) , 4-5h. ref. on a waterbath .Then cooled , filtered, washed (water), and recrystallized via ethanol. (28) (Table 1).

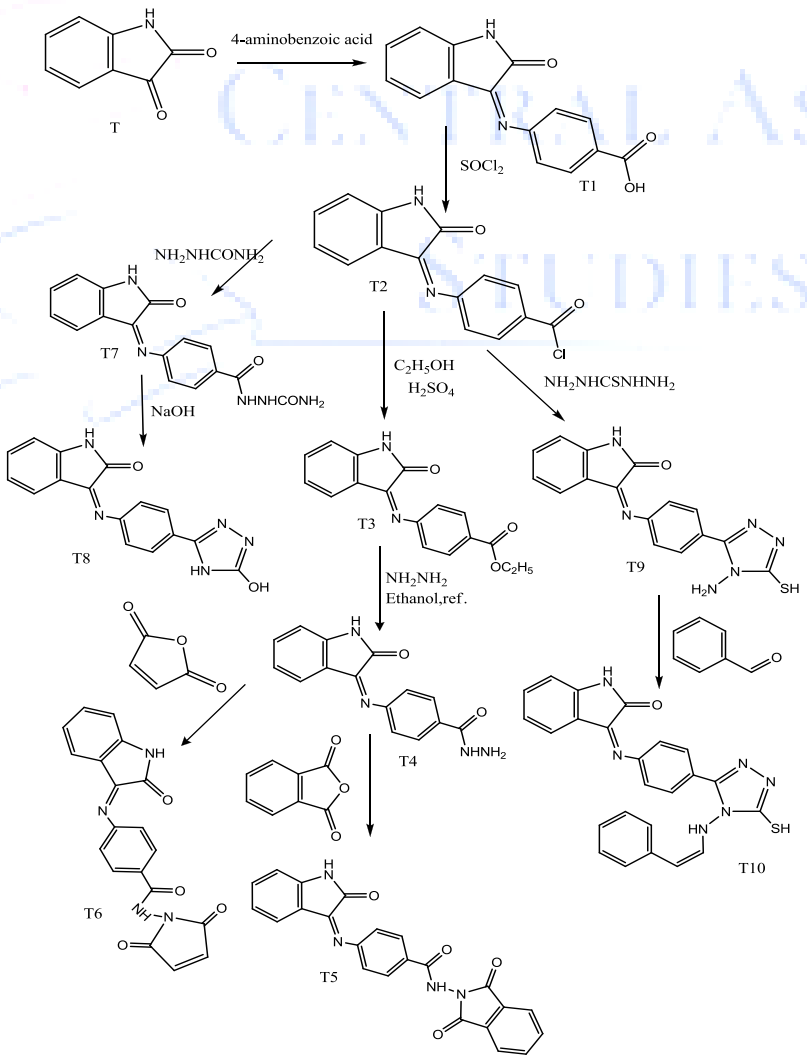
FTIR of compound T10 : 3424 (NH), 2933 (C-H al.), 3005(C-H ar.),1709 (C=O), 1577 (C=N),1421 (C=C).

1H NMR: δ 10.74 (s,1H,SH), 10.18 (s,1H,NH), 8.47(s,1H,N=CH), 8.44-8.04 (m,12H,Ar-H)..

Table 1:Some of the physical properties of compounds (T1-T10)

Com. NO.	Molecular Formula	M.Wt	Colour	m.p. ^oC	Yield %	Rf	(TLC)
T1	$C_{15}H_{10}N_2O_3$	266	Light yellow	280-282	81	0.69	ethyl acetate: n-hexane 1:3
T2	$C_{15}H_9N_2O_2Cl$	284	yellow	201-202	90	0.72	ethyl acetate: n-hexane 1:1
T3	$C_{17}H_{14}N_2O_3$	294	Orange	225-226	92	0.67	Acetone: n-hexane 1:2
T4	$C_{15}H_{12}N_4O_2$	280	White	251-252	88	0.75	Acetone:

			yellowish				n-hexane 1:1
T5	$C_{23}H_{14}N_4O_4$	410	Yellow	293-294	94	0.83	n-hexane: DCM 1:2
T6	$C_{19}H_{12}N_4O_4$	378	Orange	278-279	80	0.78	n-hexane: DCM 1: 1
T7	$C_{16}H_{13}N_5O_3$	323	Off - white	222-223	78	0.77	Acetone: n-hexane 1:2
T8	$C_{16}H_{11}N_5O_2$	305	Light brown	280-282	81	0.76	Benzene: acetone1:1
T9	$C_{16}H_{12}$ OS	336	Orange –black	288-289	75	0.88	ethyl acetate: n-hexane 1:2
T10	$C_{24}H_{18}N_6OS$	438	brown	258-259	78	0.82	ethyl acetate: n-hexane 1:2



Scheme 1: Synthesis of Compounds (T1-T10)

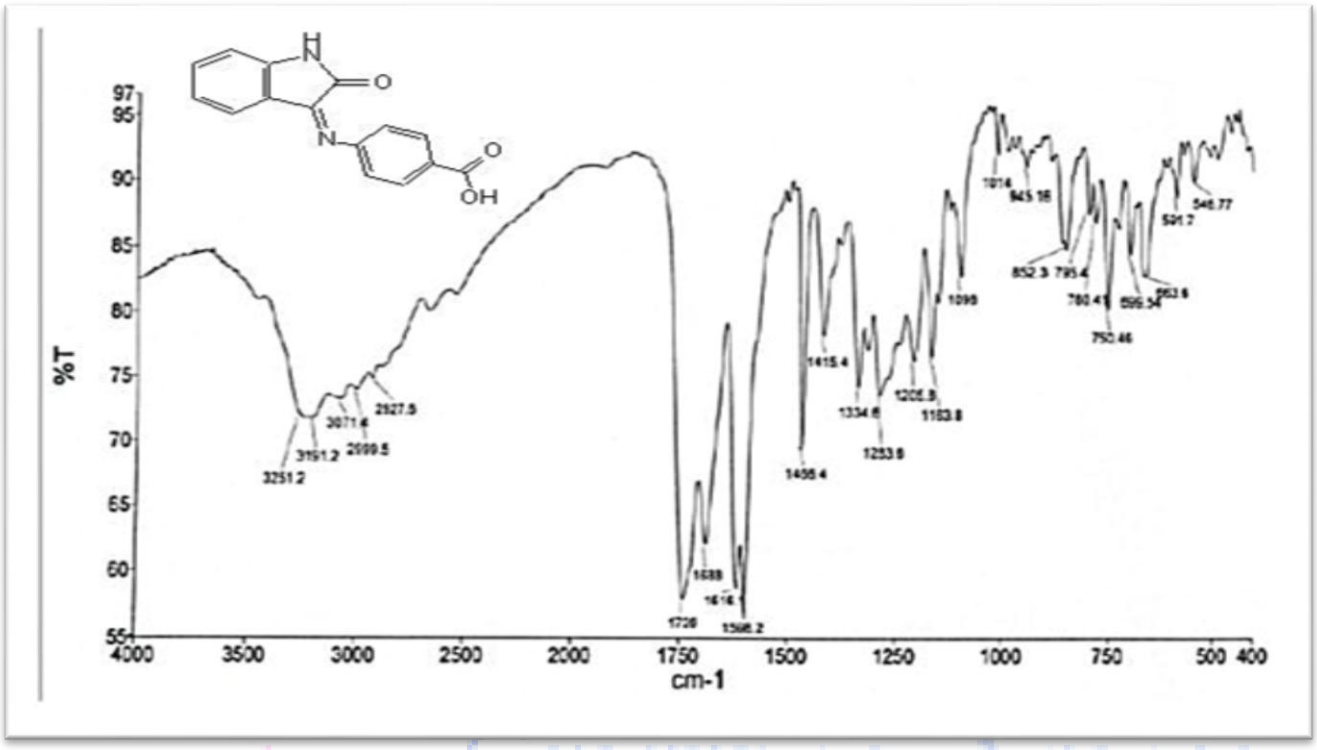


***Fig.1*: FTIR 0f compound (T1)**

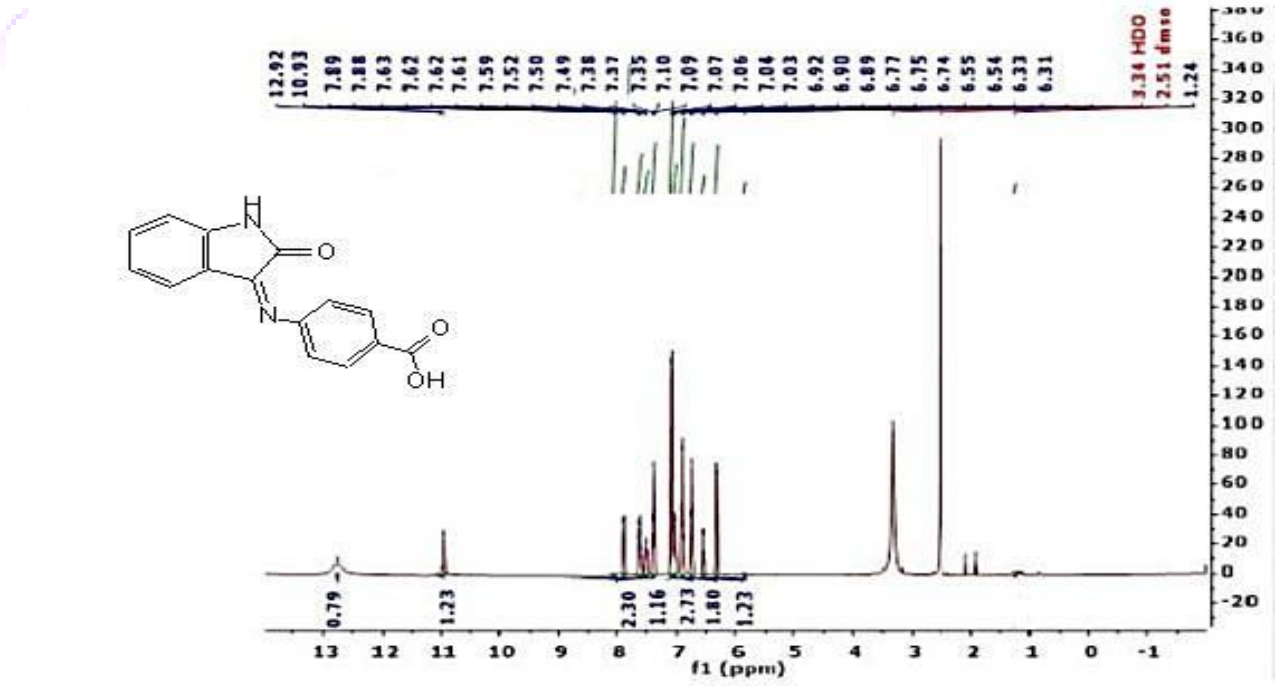


***Fig.2*: 1HNMR of compound (T1)**

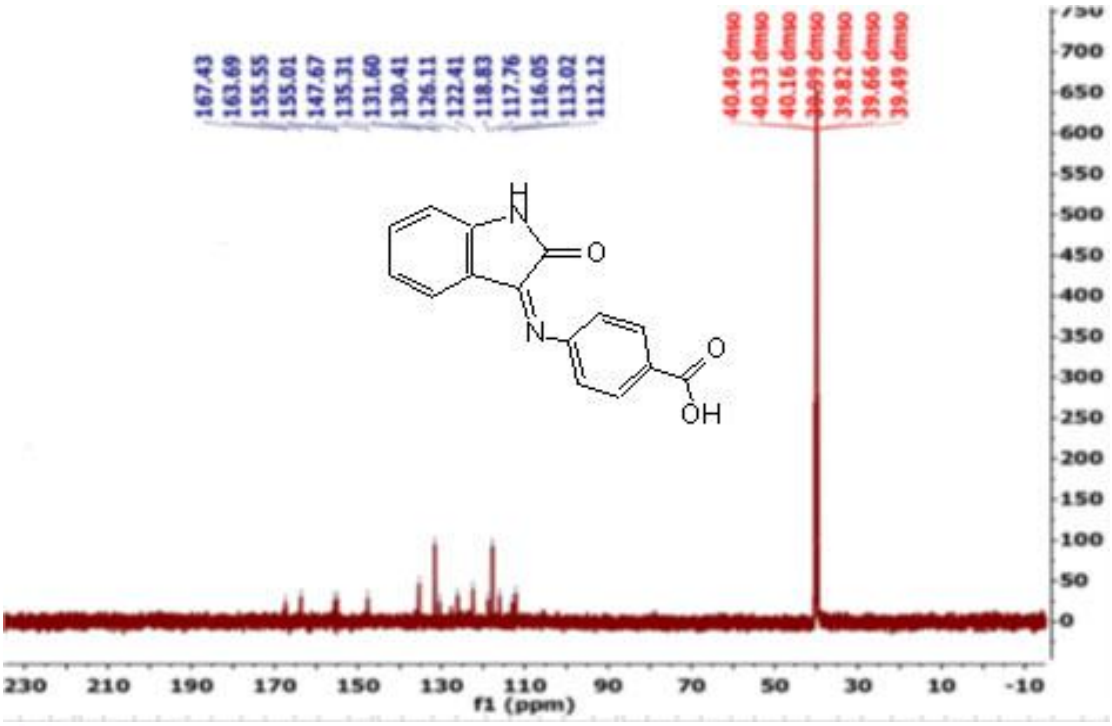


***Fig.3*: 13CNMR of compound (T1)**

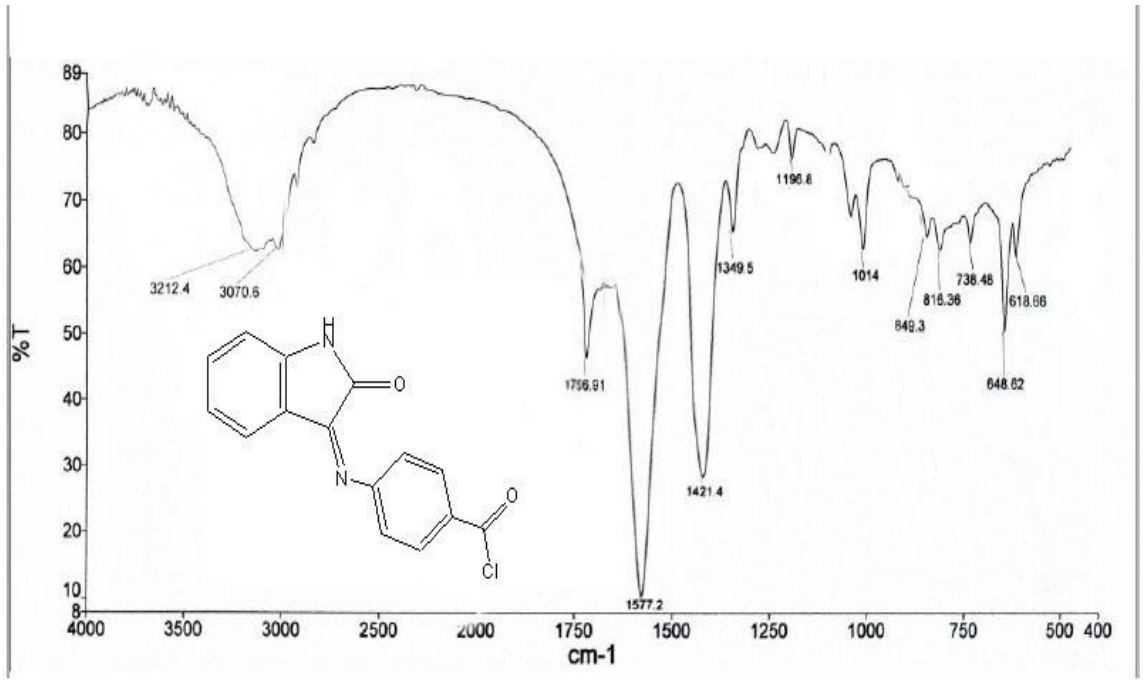


***Fig.4*: FTIR of compound (T2)**

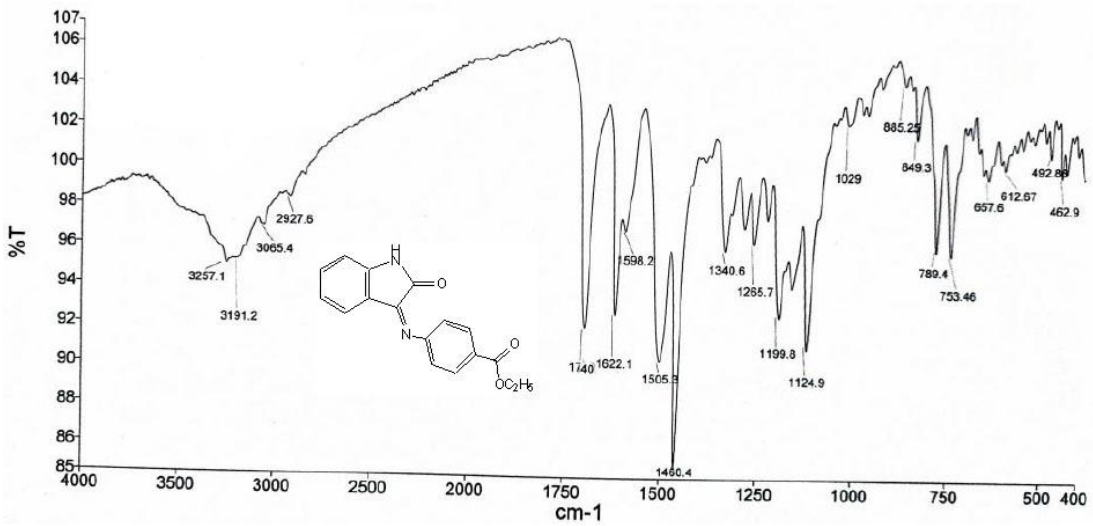


***Fig.5*: FTIR of compound (T3)**

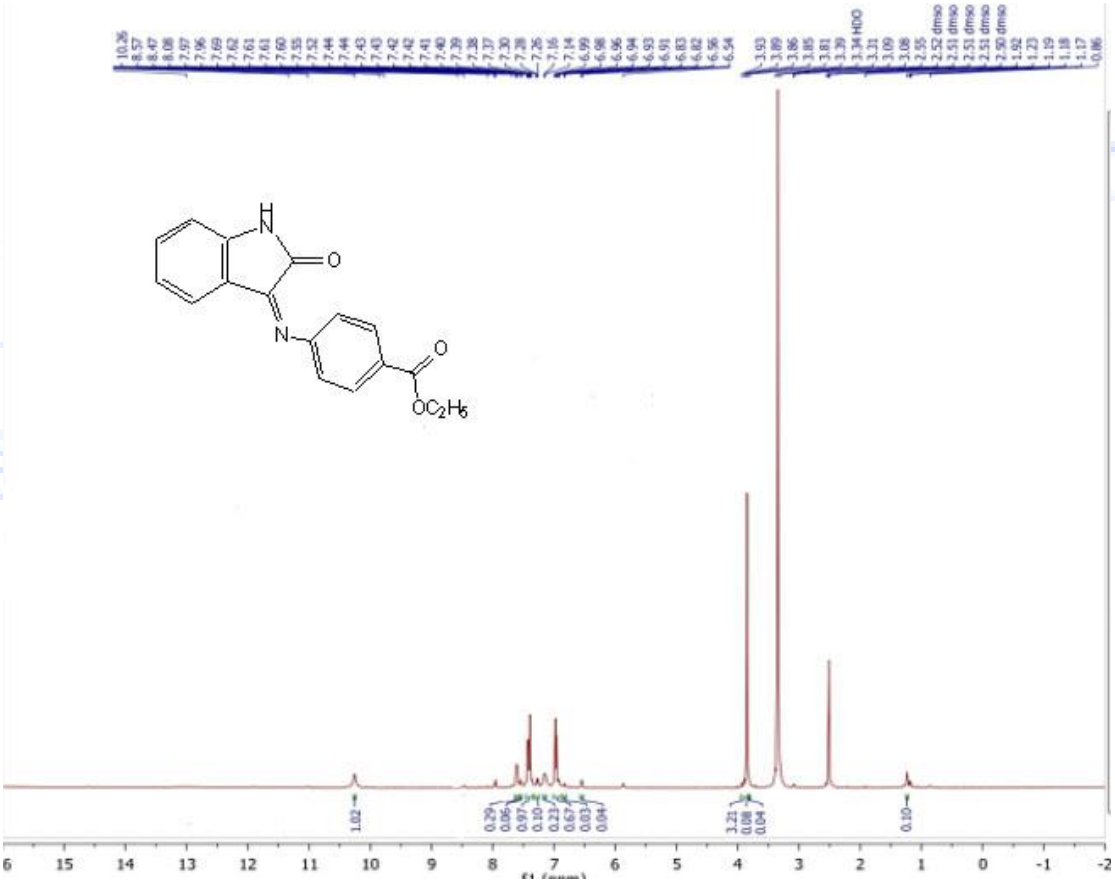


***Fig.6*: 1HNMR of compound (T3)**

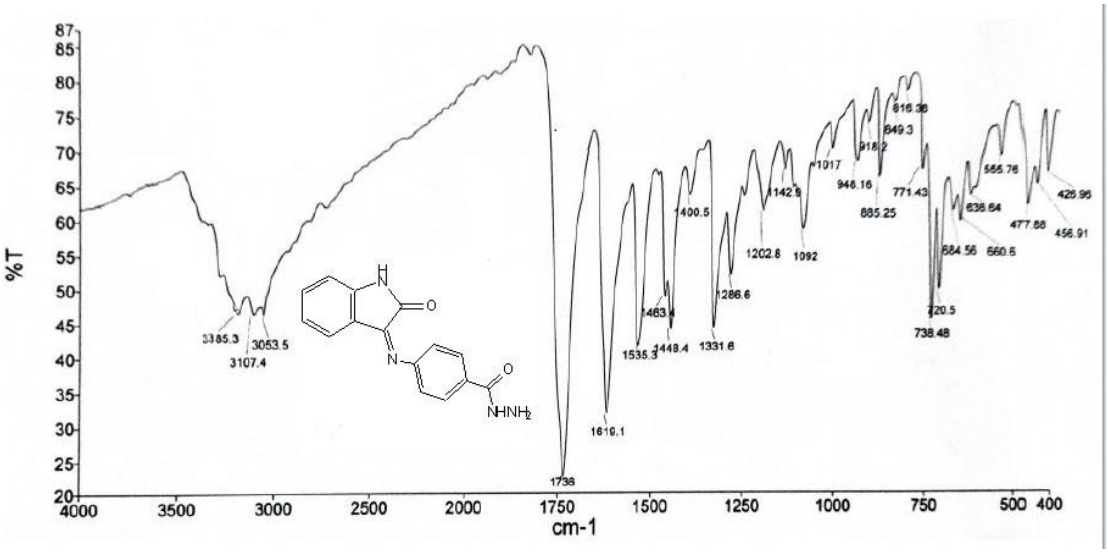


***Fig.7*: FTIR of compound (T4)**

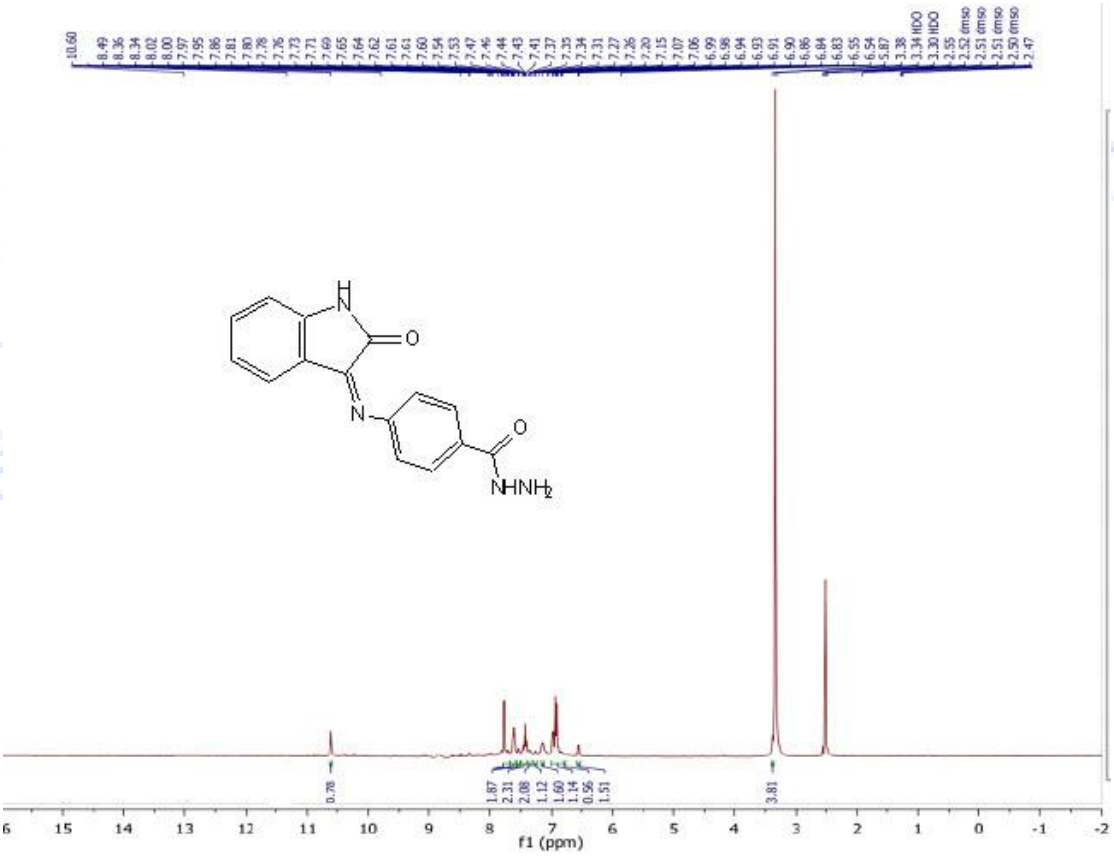


***Fig.8*: 1HNMR of compound (T4)**

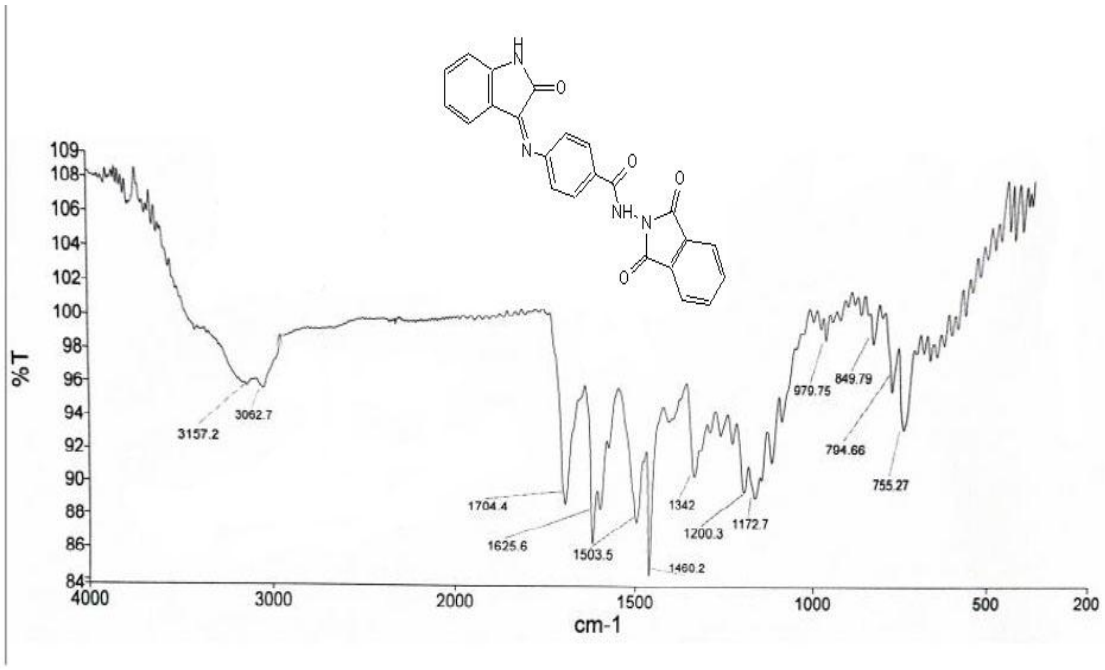


***Fig.9*: FTIR of compound (T5)**

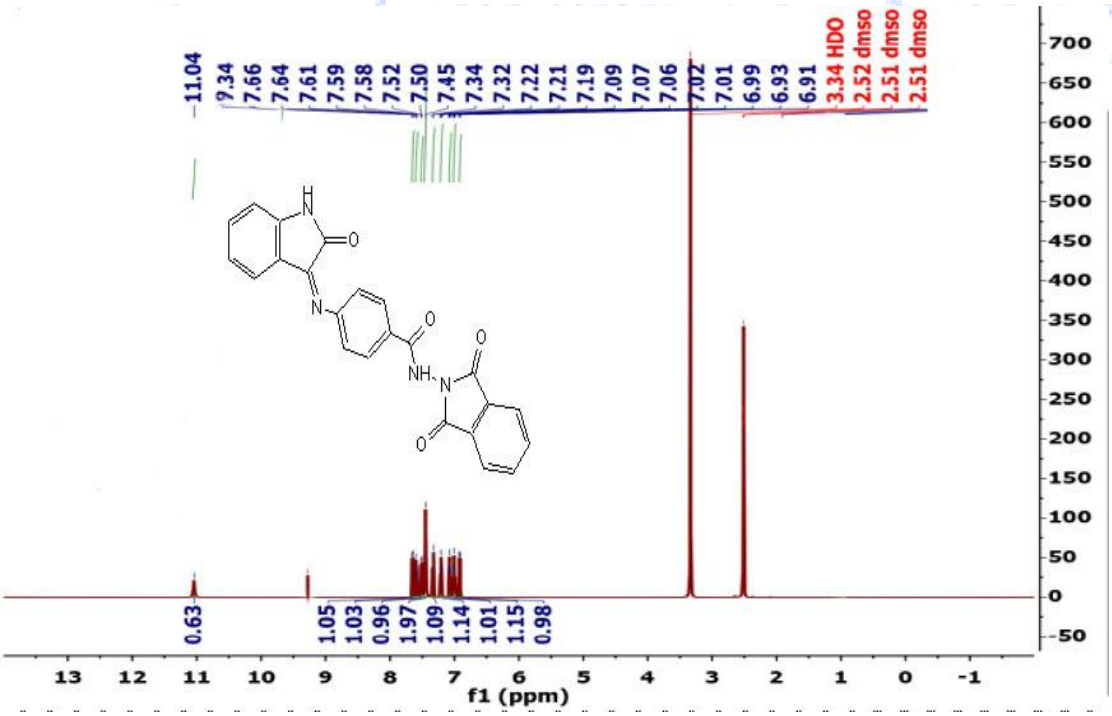


***Fig.10*: 1HNMR of compound (T5)**

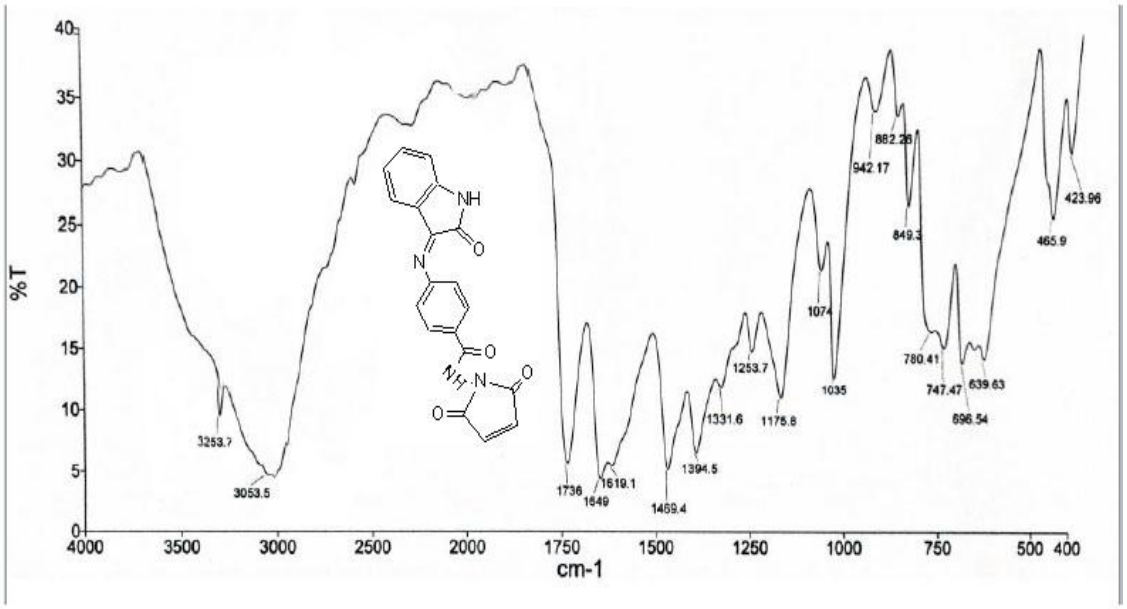


***Fig.11*: FTIR of compound (T6)**

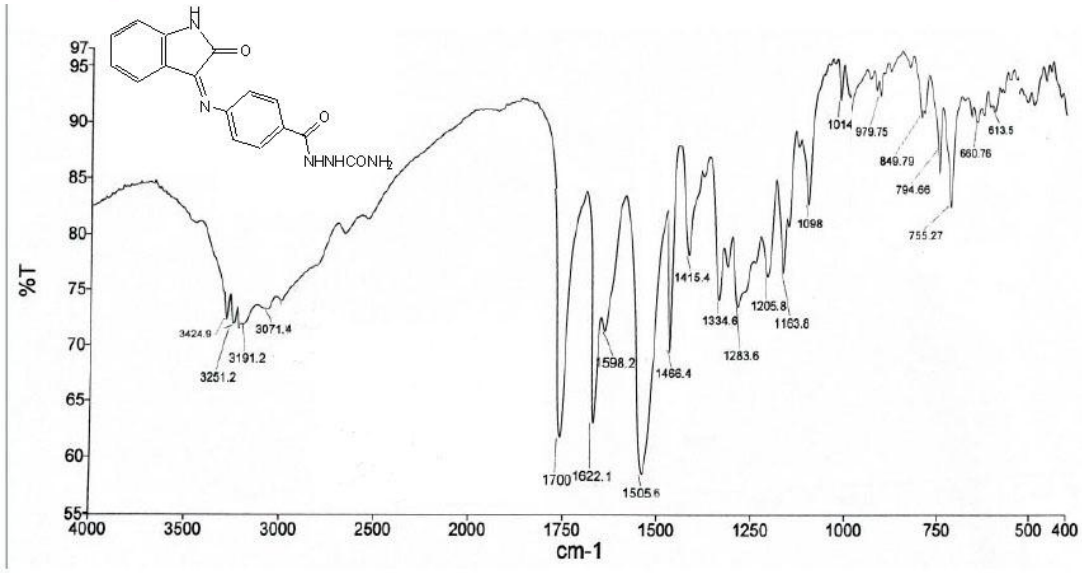


Fig.12: FTIR of compound (T7)

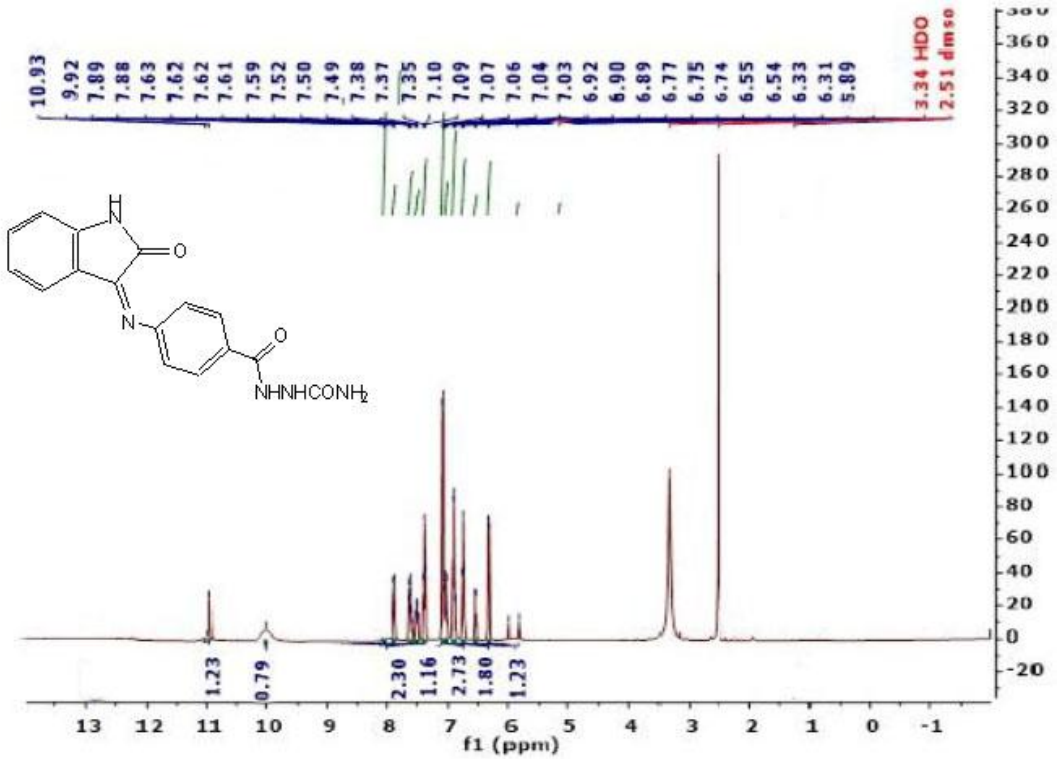


***Fig.13*: 1HNMR of compound (T7)**

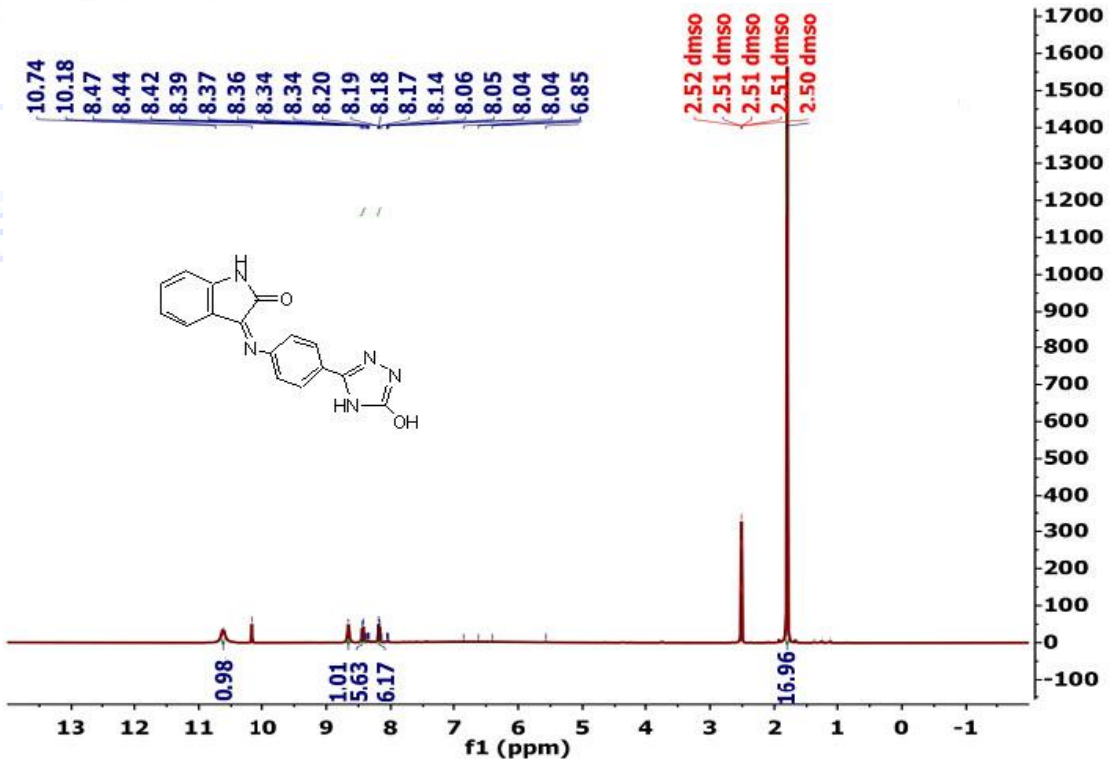


***Fig.14*: 1HNMR of compound (T8)**

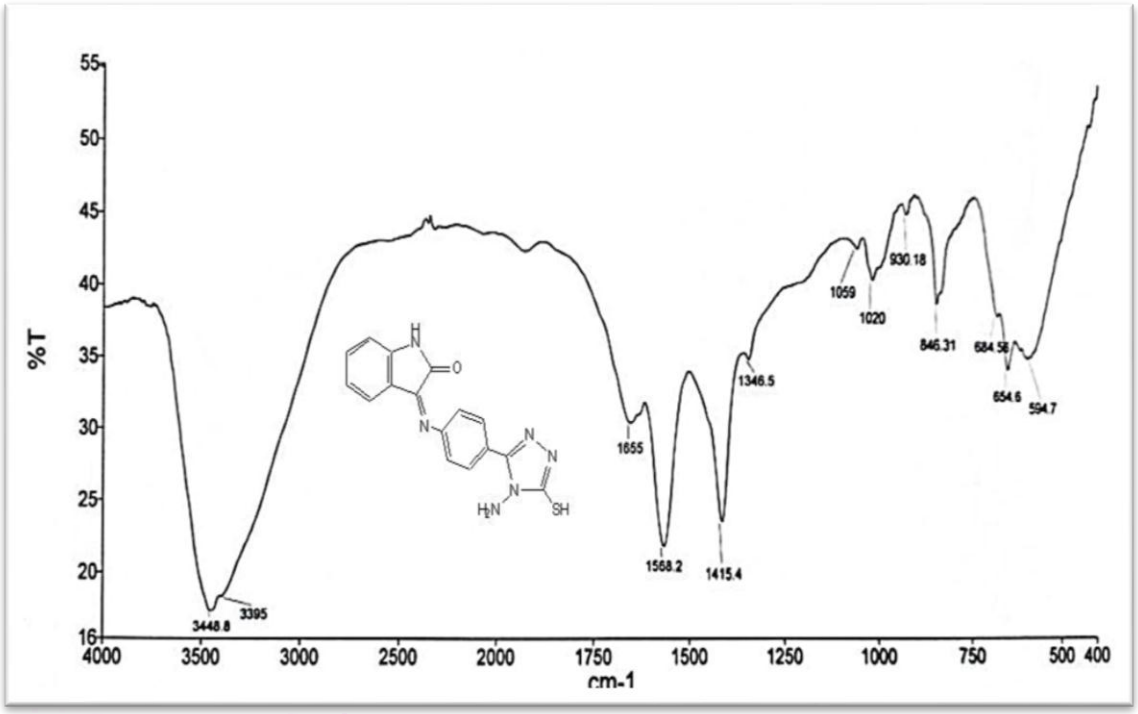


***Fig.15*: FTIR Of compound (T9)**

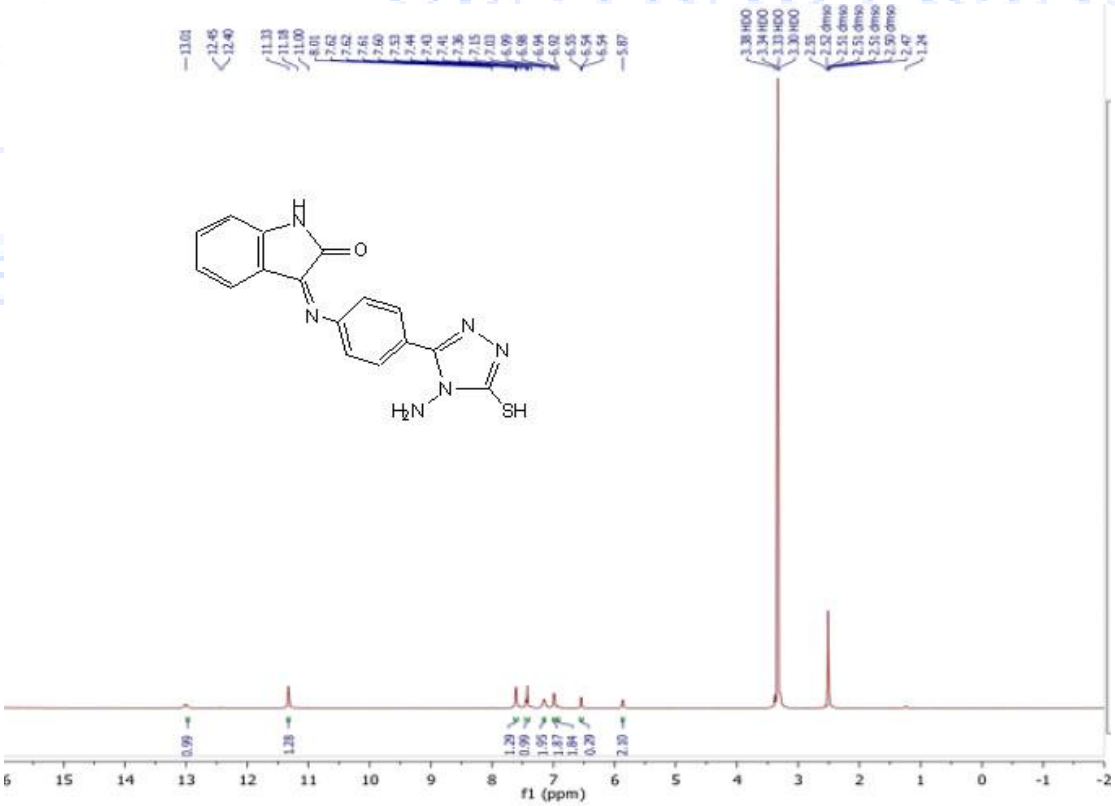


***Fig.16*: 1HNMR of compound (T9)**

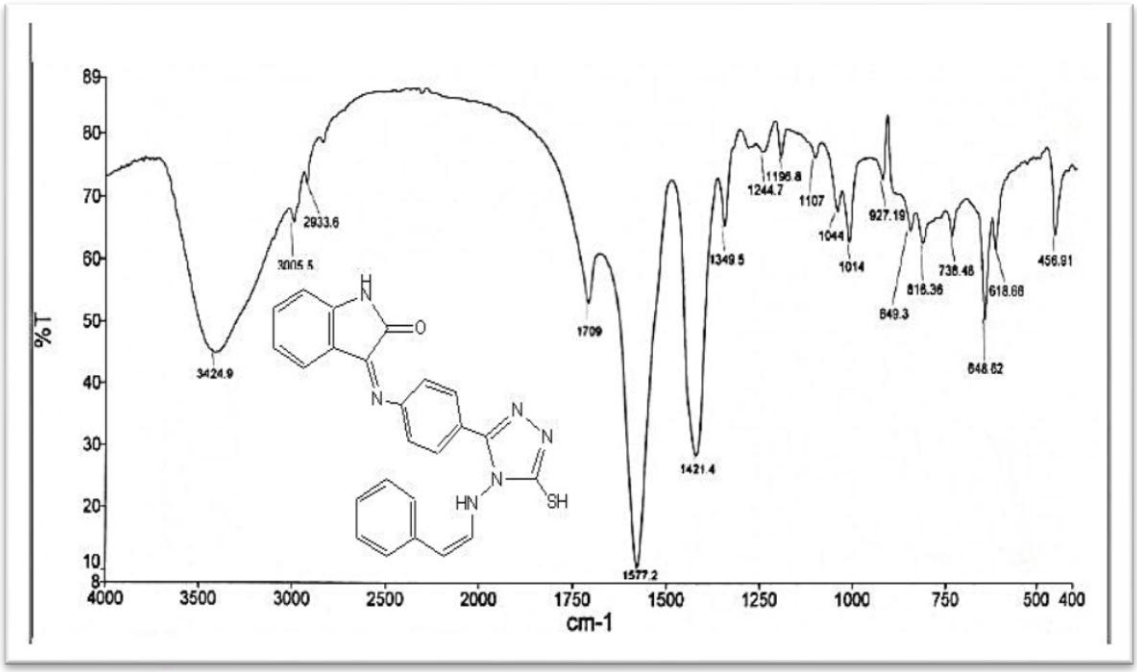


***Fig.17*: FTIR Of compound (T10)**

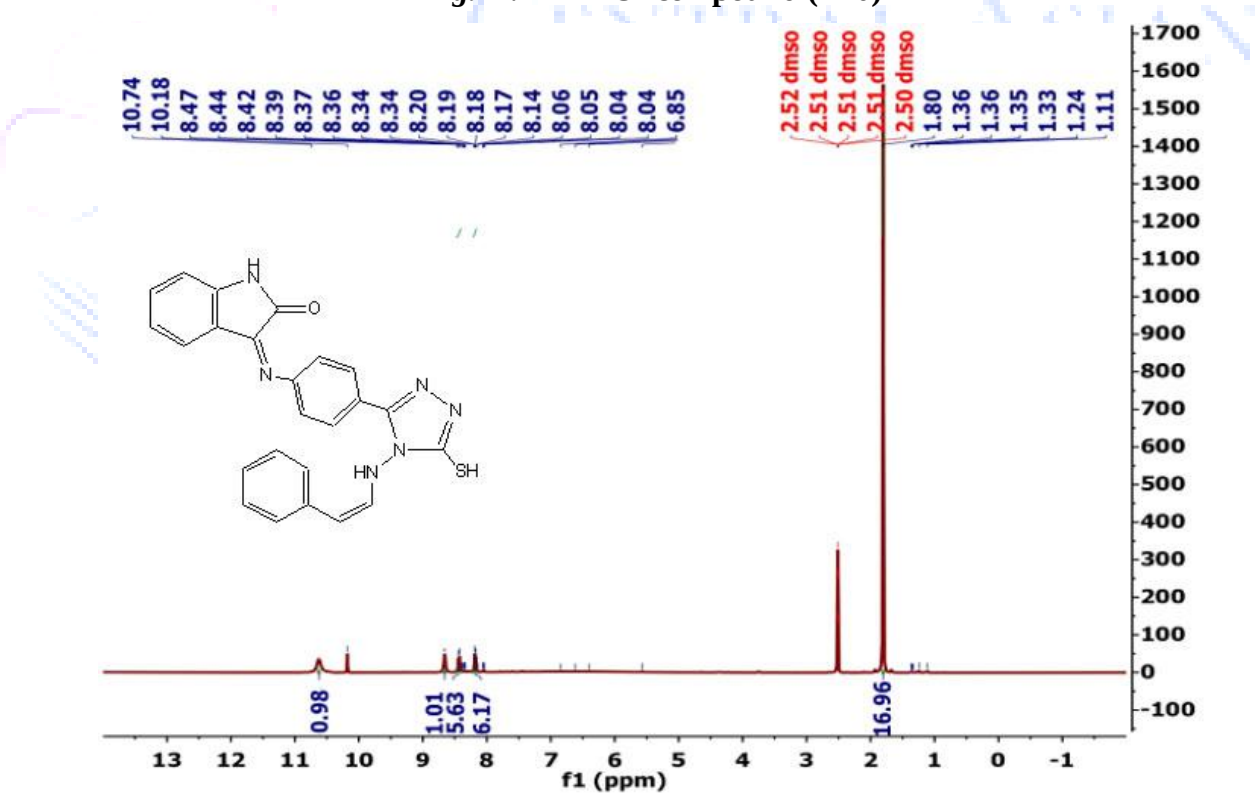


***Fig.18*: 1HNMR of compound (T10)**

3. Biological productivity

The results showed that the compounds (T2,T3.T6,T7,T8,T9,T10) had high activity against S. aureus bacteria, low activity for (T5,T4).

the compounds(T5,T6.T7) had high activity against (E. coli) bacteria, low activity for (T2,T3,T8,T9,T10).

Table 2: The biological activity of (T2-T10) compounds

Comp. No.	E-coli(G-)	Staph. Aureus(G+)
Ciprofloxacin (Antibiotic) Standard	14	12
T2	9	16
T3	12	15
T4	10	11
T5	18	10
T6	15	13
T7	14	12
T8	10	12
T9	8	16
T10	12	15

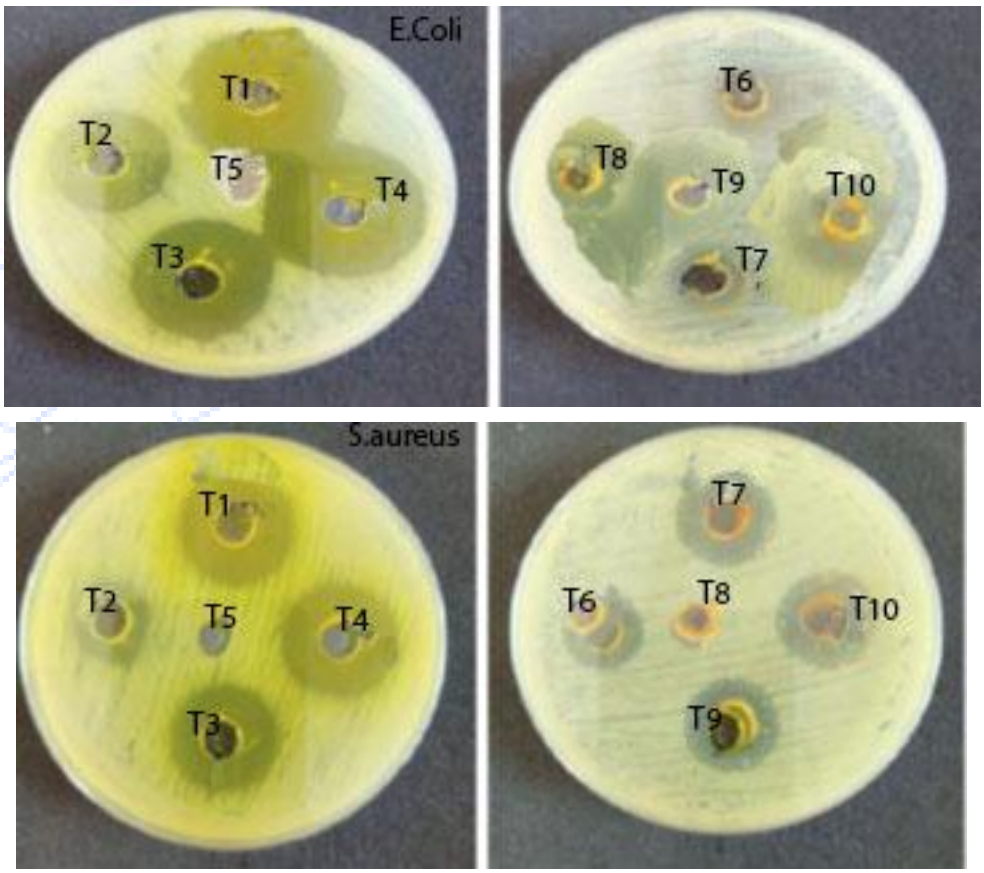


Fig. 19: Biological Effect of (T1-T10)compounds

4. Cytotoxic Action

The toxic effects of the prepared compounds(T5,T8,T9,T10) were evaluated using an MTT assay on a human breast cancer cell line (MCF7), ,it was show (T8 and T9) compounds had the most result with IC50 (25.03,28.73) comparing with control.

Table 3 :The anti-cancer activity of (T10) compound.

	concentration (µg/ml)	OD	OD	OD	average	% cell viability
	50	0.126	0.124	0.122	0.125	31.2604168
	40	0.145	0.146	0.152	0.151	35.34651682
	30	0.188	0.178	0.167	0.175	43.39267639
	20	0.277	0.234	0.286	0.266	55.45221792
	10	0.374	0.379	0.384	0.3723	69.04763322
	5	0.425	0.322	0.367	0.396	79.18725811
	2.5	0.428	0.34	0.378	0.38	89.38106579
	0	0.45	0.334	0.422	0.387	100
IC_{50}	33.13 (µg/ml)					

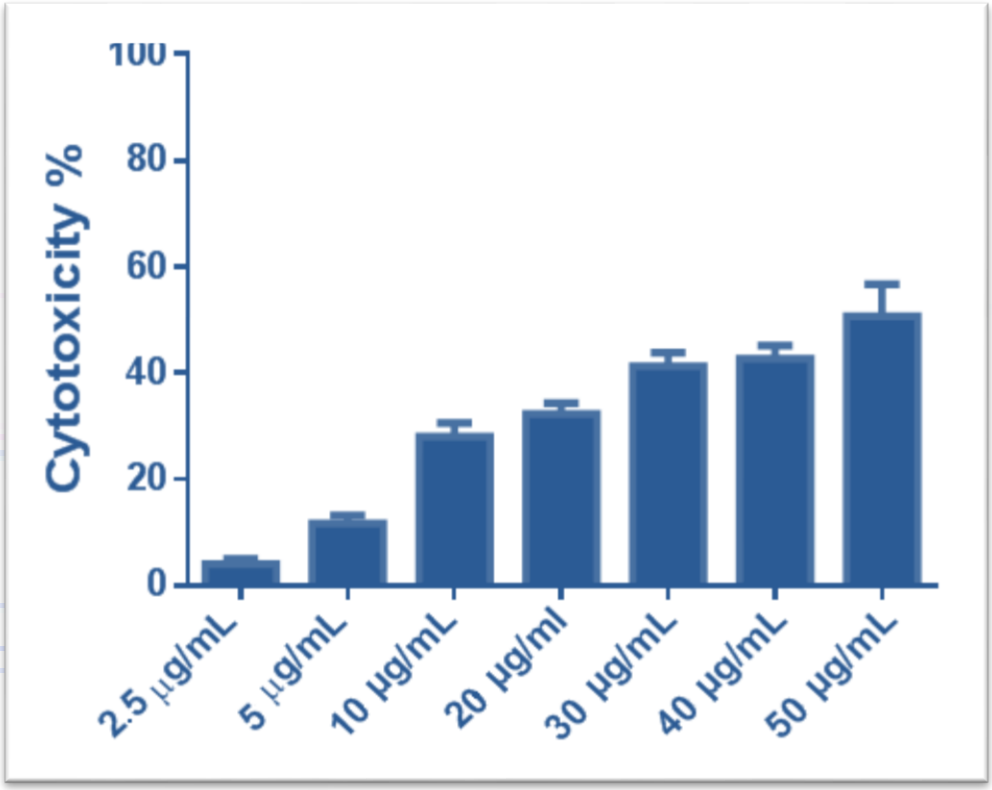


Fig.20: Cytotoxic effect of T10, IC50 = 33.13

Table 4: The anti-cancer activity of (T8) compound.

	concentration (µg/ml)	OD	OD	OD	average	% cell viability
	50	0.146	0.113	0.102	0.125	28.2604168
	40	0.125	0.143	0.132	0.121	32.45651680
	30	0.283	0.157	0.146	0.165	40.27267627
	20	0.177	0.284	0.186	0.166	46.4221732
	10	0.274	0.279	0.264	0.273	79.06763312
	5	0.305	0.352	0.337	0.336	82.25625809
	2.5	0.388	0.33	0.378	0.33	92.28106770
	0	0.44	0.414	0.352	0.397	100
IC_{50}	25003 (µg/ml)					

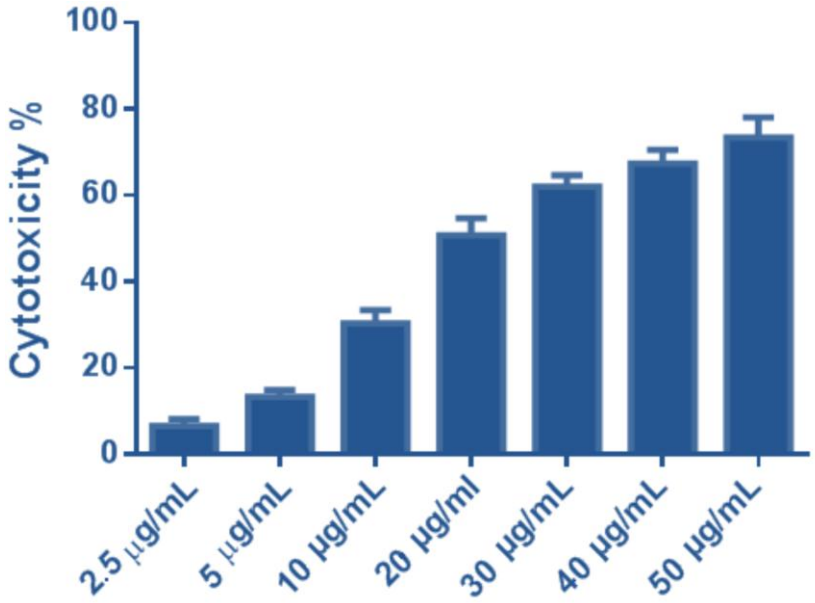


Fig.21 : Cytotoxic effect of T8, IC50 = 25.03

Table 5 :The anti-cancer activity of (T9) compound.

	concentration (µg/ml)	OD	OD	OD	average	% cell viability
	50	0.136	0.116	0.122	0.136	25.03328467
	40	0.115	0.144	0.135	0.131	28.90510949
	30	0.153	0.167	0.176	0.168	37.17435256
	20	0.277	0.284	0.296	0.266	63.4346181
	10	0.374	0.357	0.346	0.363	77.7431679
	5	0.375	0.382	0.387	0.386	82.81751825
	2.5	0.488	0.43	0.478	0.431	91.3634525
	0	0.34	0.44	0.452	0.497	100
IC_{50}	27073 (µg/ml)					

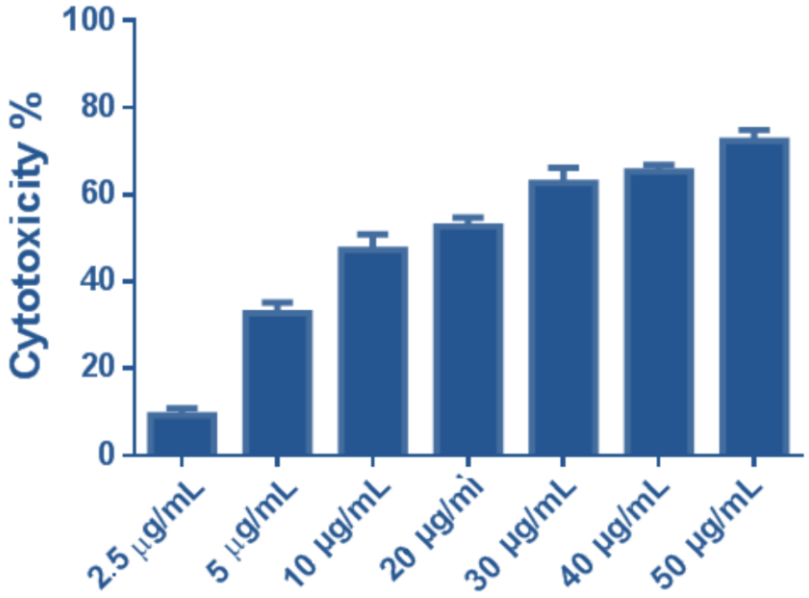


Fig.22 : Cytotoxic effect of T9, IC50 = 28.73.

Table 6 :The anti-cancer activity of (T5) compound.

	concentration (µg/ml)	OD	OD	OD	average	% cell viability
	50	0.236	0.2616	0.222	0.236	51.485394
	40	0.245	0.284	0.265	0.231	54.681383
	30	0.253	0.267	0.276	0.268	56.427670
	20	0.277	0.284	0.296	0.266	62.237438
	10	0.334	0.247	0.316	0.263	66.381338
	5	0.345	0.372	0.257	0.326	85.341630
	2.5	0.428	0.423	0.398	0.441	97.448245
	0	0.51	0.446	0.447	0.456	100
IC_{50}	55.63 (µg/ml)					

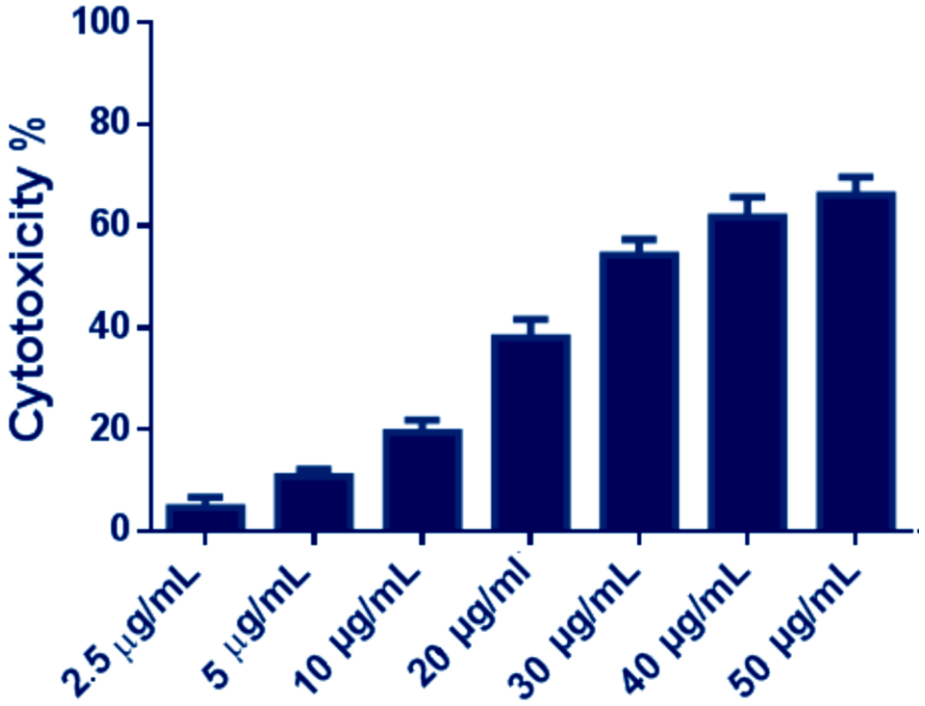


Fig.23 : Cytotoxic effect of T5, IC50 = 55.63

5. Conclusions

New heterocyclic compounds with Isatin. It has medicinal properties for drug development.Its synthesis and diagnosis.

The prepared compounds gave good results regarding antibacterial activity

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